

Supplementary Table 5. Possible impact of DDX3X mutations.

DExD-box helicases can be divided into two structural domains: a helicase ATP-binding domain (residues 211-403 in DDX3X) and a helicase C-terminal domain (residues 414-575 in DDX3X). Most DExD-box helicases contain nine consensus sequences that form the conserved core of the helicase.

Motif	Function(s) of motif	Location in DDX3X	Sequence in DDX3X
Q	RNA recognition	-	-
I	Walker A motif, crucial for ATPase and helicase activities	224-231	AQTGSGKT
Ia	RNA binding	274-279	PTRELA
Ib	RNA binding	323-327	TPGRL
II (DEAD-box)	Walker B motif, necessary for the ATPase activity	347-350	DEAD
III	May participate in linking ATPase and helicase activities	382-384	SAT
IV	RNA binding	401-407	IFLAVGT
V	RNA binding	444-455	TLVFVETKKGAD
VI	Interface between domains 1 and 2 - important for ATPase activity and RNA binding	527-534	HRIGRTGR

DDX3X mutations R276K, D354H, and R376C are in the ATP-binding domain, while mutations D506Y, R528H, R534H, and P568L are in the C-terminal domain.

Mutation	Proposed impact on DDX3X based on structural model
R276K	Part of motif Ia - an interaction with RNA may be disrupted.
D354H	Proximal to DEAD-box motif – ATP binding pocket may be disrupted.
R376C	R376 may form a hydrogen bond with the backbone amide of F396. Mutation may destroy this proposed interaction and disrupt structure.
D506Y	D506 is proximal to VI-motif residues near the interface of domains 1 and 2 - ATPase activity and/or RNA binding may be disrupted.
R528H	R528 is part of the VI-motif – ATPase activity and/or RNA binding may be disrupted.
R534H	R534 is part of the VI-motif – ATPase activity and/or RNA binding may be disrupted.
P568L	Loss of proline may result in extension of the helix into Serine-rich sequence.

I motif

(220)LMAC**AQTGSGKTA**AFLLPILSQIYSDGPGEALRAMKENG~~R~~YGRRKQYPISLVLA**P**TRELAVQIYEE

Ib motif

ARKFSYRSRVRPCVVYGGADIG**Q**OIRDLERGCHLLVA**T**PGR**I**VDMMERGKIGLDFCKYLVL**D**EAD**R**M**L**D**M**G

III motif *IV motif*

FEP**Q**IRRIVEQDTMPPKG**V**H**T**MMF**S**ATFPKEI**Q**MLARDFLDEY**I**FLAVGRVGSTSENIT**Q**KVVWVEESDK

V motif

RSFLLDLLNATGKDSL**T**L**V**FVETKKG**A**DSLEDFLYHEGYACTSIHGDRS**Q**RDREEALHQFRSGKSPILVAT

VI motif

D**506**Y R**528**H R**534**H P**568**L

AVAARG**L****D**ISNVKHVINFDLPSDIEYV**H****I**GR**T****G****R**VGNLGLATSFFNERNNINIT**K**DL**D**LL**V**EAK**Q**EV**P****S**

WLENMAYEH**H**YKGSSRGRSKSSRFSGGF**G**ARDY**R**QSSGASSSSFSSSRASSSRGGGGHGSSRGFGGGGYG

GFYNNSDG**Y**GGNYNSQGV**D**WWGN (662)

